Necrosis

Introduction

Necrosis is what happens to a cell when it suffers an injury it cannot tolerate, resulting in a sequence of events that are **unprogrammed**, unexpected, and uncontained. Necrosis is cell death. It's messy (**inflammation** is present) and **always pathologic**. It's caused by the **loss of homeostasis**. The way a cell dies from a lethal insult may vary between cells and between insults. Ultimately, the cell ceases to function and any leftover pieces are swept up by the immune system. In general, necrosis is separated from apoptosis, at least microscopically, by several features.

NECROSIS	APOPTOSIS
Large, contiguous patches of cells all dying together	A single cell (adult life) or small cluster (embryogenesis)
Swelling of the cell membrane	Shrinkage
Disrupted membrane (lysis)	Intact membrane (no lysis)
Cytoplasm release causes lots of inflammation	Cytoplasm contained, so no inflammation
Pyknosis (gets smaller), karyolysis (fades), and karyorrhexis (fragments)	Pyknosis and karyolysis, but no karyorrhexis
Everything fragments	No fragmentation
Histology shows intact cytoarchitecture without proteins, ribosomes, or dark-staining material	Cell slowly takes itself apart, piece by piece
Neutrophils, lymphocytes	No immune cells

Table 2.1: Necrosis vs. Apoptosis
This is obligatory because all students expect it. We do not recommend comparing and contrasting them, but rather learning them as discrete topics without overlap.

In necrosis, there are no pathways to remember, no enzymes to engage. Instead, we will study the different **types of necrosis** and the multiple **stages of coagulative necrosis**.

Nuclear Changes

Both pyknosis and karyolysis are seen in both necrosis and apoptosis. **Pyknosis** describes the nucleus's getting smaller, representing DNA condensing into shrunken particles. **Karyolysis** describes the fading away of the nuclear envelope and nuclear material, characterized by chromatin dissolution due to DNAases and RNAases. **Karyorrhexis** describes nuclear fragmentation. **All three features** occur in necrosis.

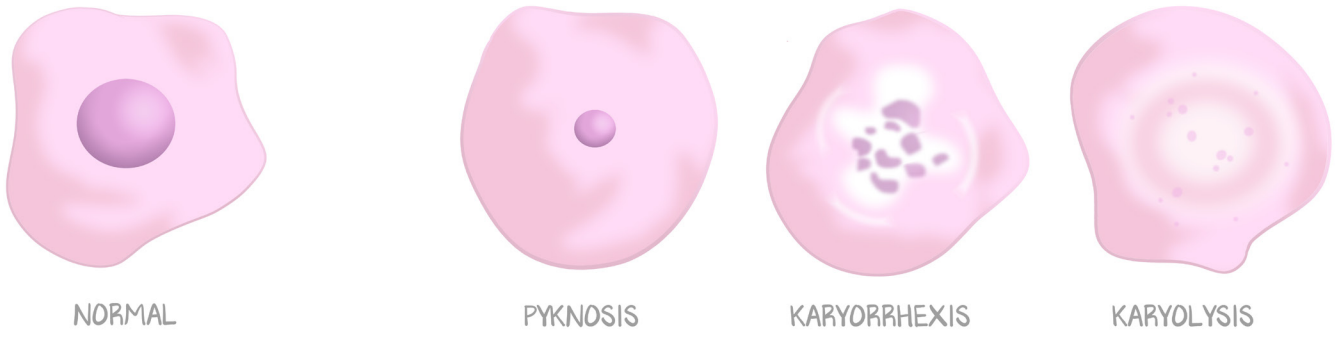
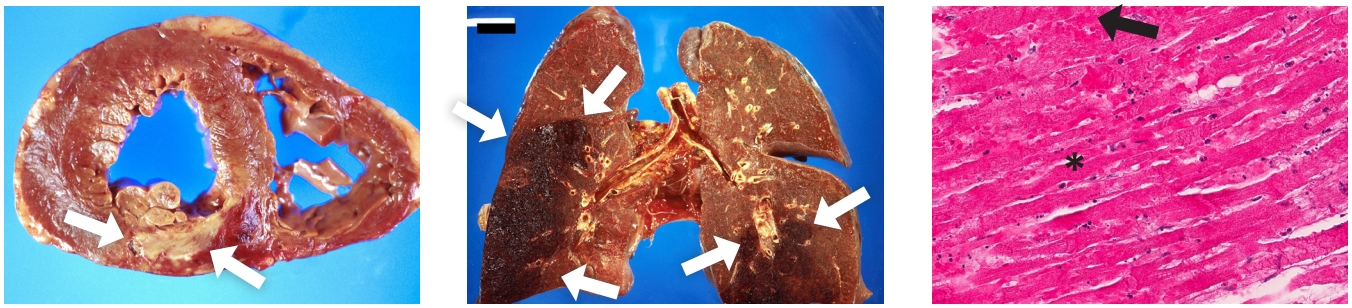


Figure 2.1: Nuclear Changes
Artist's rendition of the different nuclear changes. The normal nucleus undergoes any or all of these changes during necrosis. It can appear to shrink (pyknosis), fracture (karyorrhexis), and/or fade away (karyolysis).

Types of Necrosis

The cause of necrosis helps inform the predominant pathology. In tissue that becomes hypoxemic and that has glycogen, lactic acidosis and denaturation predominate. In tissue that either doesn't have glycogen (CNS) or dies because of an infection (pyogenic bacteria), lysis will predominate. And then there are special types of necrosis—saponification of adipose, caseating granulomas of TB, fibrinoid necrosis of vasculitis.

Coagulative necrosis is a result of ischemia, of poor tissue perfusion. When blood (oxygen) fails to reach an organ, the cells can no longer rely on oxidative phosphorylation. They switch to anaerobic metabolism, shunting any glucose they have (their glycogen) to lactate. Lactic acid accumulates and the pH of the cell drops. The drop in the pH causes **denaturation of proteins**. That denaturation of proteins causes **ribosomes to disaggregate**, cytoplasmic proteins to denature, **lysozymes to denature**, and the nuclear envelope to fall apart. It is because the pH drops first that denaturation of proteins predominates rather than lysis of the cells by lysosomal enzymes. Because lysosomes have enzymes, and enzymes are proteins, and protein denaturation predominates, coagulative necrosis does NOT demonstrate **autolysis** (destruction caused by enzymes from the cell's own lysosomes). Eventually a **scar** will form, as neutrophils clear debris, macrophages clear everything, and fibrolasts replace it with collagen (Lesson #4: *Wound Healing*). Tissue that can regenerate will. Tissue that cannot regenerate (permanent cells) will merely scar. But because there is no autolysis, until neutrophilis replace the dead cells, the general cellular architecture is intact. On gross, these tissues will be **hard to touch**, and will have either white regions (**pale** or nonhemorrhagic) or red regions (**hemorrhagic**). On micro, there will be **normal cellular architecture** but **absent nuclei**, absent ribosomes, and **the cells stain intensely pink** (they lose their blue color because proteins denature and the nuclear material is digested).



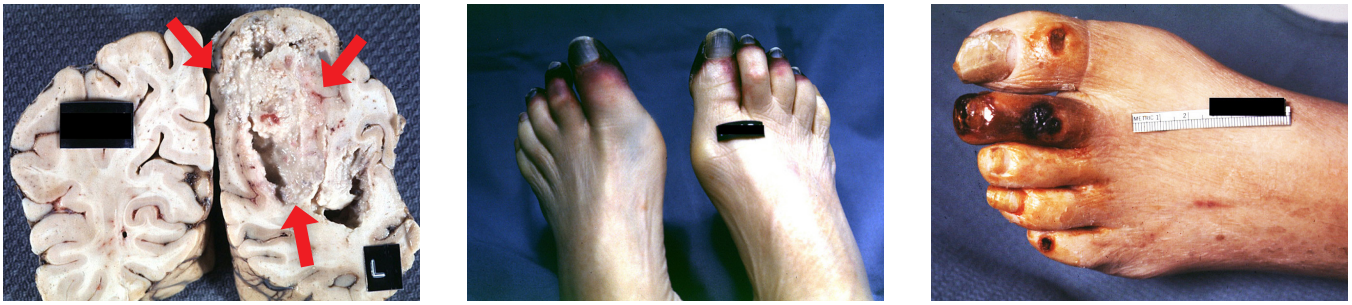
(a) (b) (c)

Figure 2.2: Coagulative Necrosis
(a) Pale infarction. Cross section of a heart obtained at autopsy from a patient who suffered an acute myocardial infarction, resulting in coagulation necrosis of the posterior wall and development of a pale infarct (arrows). (b) Red infarction. Multiple pulmonary thromboemboli resulted in several infarctions in these lungs (arrows). (c) Coagulation necrosis due to a myocardial infarction. The heart muscle is really pink (eosinophilic), there is not much blue (no ribosomes and few nuclei) Healthy tissue is at the lower right of the asterisk. Diseased tissue is labeled by the arrow, showing loss of nuclei.

Liquefactive necrosis is seen in infarctions of the **central nervous system** and **pyogenic infections**, such as **wet gangrene**. Liquefactive necrosis tends to have a wet, amorphous, viscous appearance on gross (the architecture of the organ is lost and it looks like soup). The mechanism behind liquification is less from the lactic acidosis and protein denaturation of coagulative necrosis and more due to the release of digestive enzymes. These digestive enzymes degrade both the microscopic and gross tissue into that soup. Although **autolysis** is destruction of a cell by its own digestive enzymes, when those enzymes come from pyogenic bacteria (from the bacteria themselves) or from the neutrophils (the inflammatory response to the bacteria), it's called **heterolysis**.

The CNS has no glycogen, so poor perfusion (now of both oxygen and glucose) means not only the loss of oxidative phosphorylation but also the loss of glycolysis of any kind. Without glycolysis, there can be no lactic acidosis, no decrease in pH, and no denaturation of proteins. Which means **digestion predominates** (autolysis). Pyogenic infection means "neutrophilic infection." Neutrophils release digestive enzymes to kill the bacteria. Those digestive enzymes will also damage good cells near the bacteria. Even the bacteria themselves can release digestive enzymes. Either way, in the affected tissue cells die and **digestion predominates** (heterolysis).

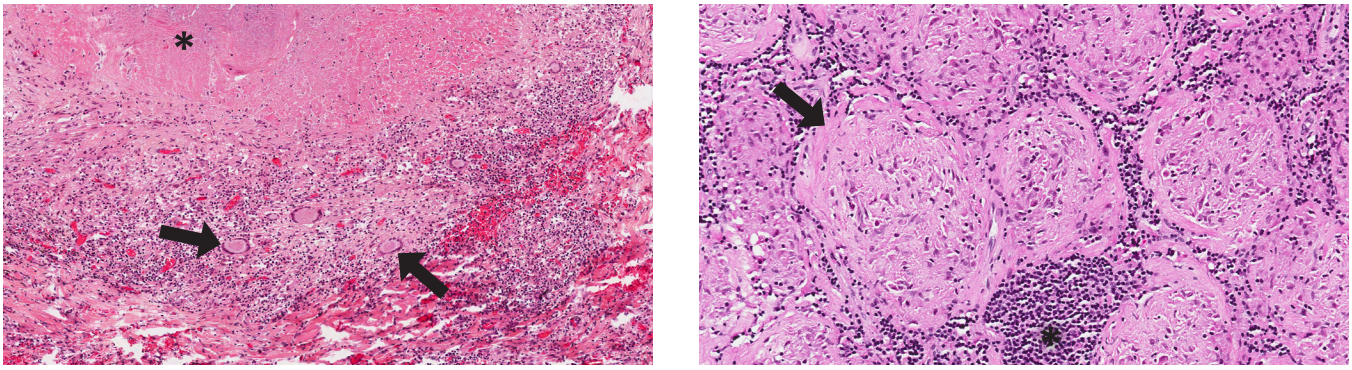
Dry vs. wet gangrene. Gangrene is a term used to describe what's affecting a necrotic organ—like a foot. **Dry gangrene** is caused by poor tissue perfusion (the cells will appear to have coagulative necrosis). **Wet gangrene** is the poor tissue perfusion of dry gangrene plus a **pyogenic infection** in the tissue leading to liquefactive necrosis. A limb may be dead and black, but not infected (dry gangrene). If that dry gangrene gets superinfected and becomes a suppurative infection, it becomes wet gangrene.



(a) (b) (c)

Figure 2.3: Liquefactive Necrosis
(a) Gross pathology of a CNS infarction demonstrating liquefactive necrosis, wherein the architecture of the organ is lost and turns to liquid. (b) Dry gangrene is coagulative necrosis of an organ, commonly seen in the extremities and caused by poor blood flow. (c) Wet gangrene has a sheen, making it look wet, and represents suppurative infection superimposed on coagulative necrosis. This is a surgical emergency.

Caseating necrosis is said to be "a combination of liquefactive and coagulative necrosis." That isn't all that helpful because it doesn't really look like either on micro or gross. It's called caseating because the gross sample will appear "cheese-like," a soft, granular, **yellowish** appearance. This is a result of the **lipids** from the cell walls of **tuberculosis** (99% of caseating granulomas on the test) or from the cell walls of systemic fungi. On microscopy, TB will be a caseating granuloma as evidenced by the **multinucleated giant cells**. There will be a dense circular area of **pink without any nuclei** (it's necrotic) surrounded by intensely staining **blue lymphocytes**. This is the "walling off" of the mycobacterium. Noncaseating granulomas (which means microscopically there are granulomas but no necrosis) can be a sign of a host of inflammatory diseases. If there are nuclei, it's not necrosis. If there's a big sheet of pink surrounded by blue nuclei, it's necrosis. There are also noncaseating granulomas which have the same granuloma material, but without the lymphocytes.

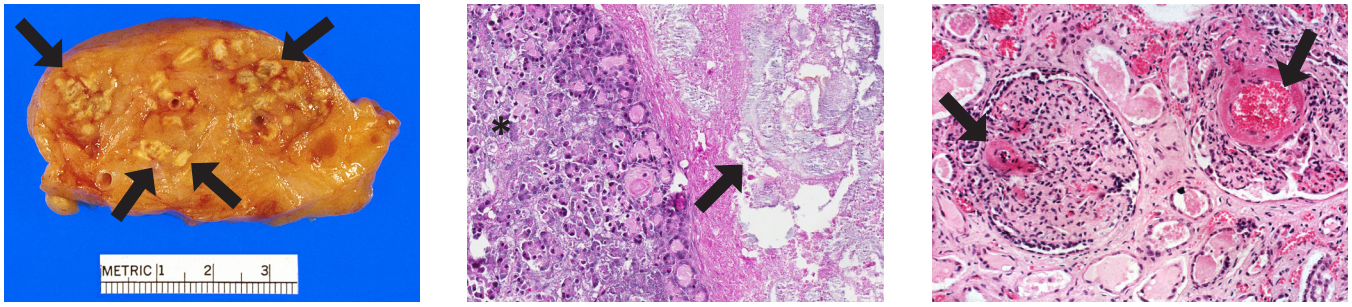


(a) (b)

Figure 2.4: Caseating Necrosis
(a) Pulmonary tuberculosis with focal areas of tuberculous infection. High-powered view showing the central area of caseous necrosis (asterisk) and the surrounding macrophages, Langhans-type multinucleated giant cells (arrows). (B) These granulomas comprise aggregates of epithelioid macrophages surrounded by a collar of lymphocytes. There is no central area of necrosis.

Fat necrosis occurs in fatty tissue. Fat necrosis is termed either enzymatic or nonenzymatic. **Nonenzymatic** is caused by **trauma**, such as in trauma to breast tissue (trauma causes rupture of the cells and the cells die). **Enzymatic** fat necrosis is a product of **lipase autodigestion** in **acute pancreatitis**. On gross, the normally yellow fat will be seen as **white and chalky**, from a process called **saponification** caused by the combination of the fats and calcium. Triglycerides within the adipose cells are hydrolyzed to their constituents: glycerol and fatty acids. A fatty acid added to a salt is how soap

is created. Fatty acid (fat) + calcium (salt) = saponification (soap). On micro, the fat cells are swollen, surrounded by lymphocytes, and take on a cloudy appearance. Anything that stains within an adipose cell is likely to be that soap.



(a) (b) (c)

Figure 2.5: Fat Necrosis and Fibrinoid Necrosis
(a) Pancreatic fat necrosis. White plaques within the pancreatic parenchyma represent areas of fat saponification (thin arrows). Necrosis of the pancreas is also evident in this section (block arrows). (b) Section of pancreas with fat tissue between pancreatic lobules. Areas of pancreatic necrosis (asterisks) are present along with saponification of the adipose tissue (arrows). (c) Fibrinoid necrosis in the kidney. Areas of fibrinoid necrosis (arrows) can be seen in the walls of arteries in these glomeruli. The vessels are thickened by deposits of antigen-and-antibody immune complexes with fibrin that leaks out of the damaged vessels. This results in a bright pink amorphous appearance on this H&E stain, referred to as "fibrinoid" or fibrin-like.

Fibrinoid necrosis is a **vascular necrosis**—diagnose fibrinoid necrosis only on a microscopic slide that contains an arteriole. It's also the easiest to spot. With vascular inflammation (**vasculitis**, **organ transplant rejection**, etc.), an artery or arteriole will be accompanied by pink material that's not supposed to be there. And the RBCs in the middle are surrounded by a dense pack of blue cells (the inflammatory cells). Don't be tricked: sarcoid is an inflammatory disorder that presents with noncaseating granulomas. Not all inflammation results in fibrinoid necrosis, but the inflammatory disorders of the blood vessels will lead to fibrinoid necrosis.

Stages of Coagulative Necrosis

Poor tissue perfusion results in insufficient oxygen. Aerobic metabolism utilizing the electron transport chain switches to anaerobic metabolism. Glucose is burned to pyruvate, but then to lactate. Without oxygen to generate ATP, the Na^+/K^+-ATPase cannot function. The membrane potential is compromised. Ions cannot be moved against their concentration gradients and homeostasis is lost. Channels cannot open. Water moves to balance osmotic forces. Water moves in, causing swelling.

Early reversible necrosis is represented by **organelle swelling**. Membrane integrity is compromised by the loss of Na^+/K^+-ATPase. Water enters the cell and crosses into organelles. **Mitochondria** and the **smooth endoplasmic reticulum swell first**. Ribosomes detach from the RER in a process called **disaggregation**. Anaerobic metabolism produces **lactic acid,** making the intracellular space acidotic (though the plasma membranes are intact, so the pH falls only in the cytoplasm or organelles). The falling pH within the cytoplasm causes **proteins to denature**. Mitochondrial swelling and disruption can result in the release of apoptotic initiators (cytochrome c), which will hasten cell death. At this point, if the insult is removed, oxygen and glucose are restored, and, perfusion maintained, the cell can recover. It's the loss of membrane integrity that marks irreversible changes.

Late reversible necrosis is the cell just before it ruptures, and is categorized by **membrane swelling**. More water has entered the cell (all organelles are swollen, and now the cell is so swollen that even the membrane is ready to burst). **Blebbing** of the cytoplasm and nuclear membrane occurs.

Lysosomes rupture, releasing their digestive enzymes, which leads to the destruction of all proteins, **proteolysis**, which causes the loss of dark blue stain on light microscopy) while **phospholipases** degrade the cell membrane (made of phospholipids). Histologically, **vesicle membranes disappear**, leaving empty **vacuoles** in the cytoplasm. The cells are described as being "**moth-eaten**." The cell could reverse and be salvaged, though autolysis and cell-membrane blebbing indicate that the death stroke is around the corner.

Irreversible necrosis is a result of **cell-membrane perforation**. As perforation occurs, two things happen: extracellular calcium enters and cytoplasm exits. **Influx of calcium**, normally a highly regulated second messenger, now rushes in and activates **Endonucleases**, **proteases**, and **phospholipases** which start degrading everything. **Mitochondrial bodies** form as a result of the calcium influx into mitochondria. The **release of the cytoplasm** into the extracellular space induces a strong **immune reaction**, summoning first neutrophils and then macrophages which secrete digestive enzymes of their own (heterolysis).

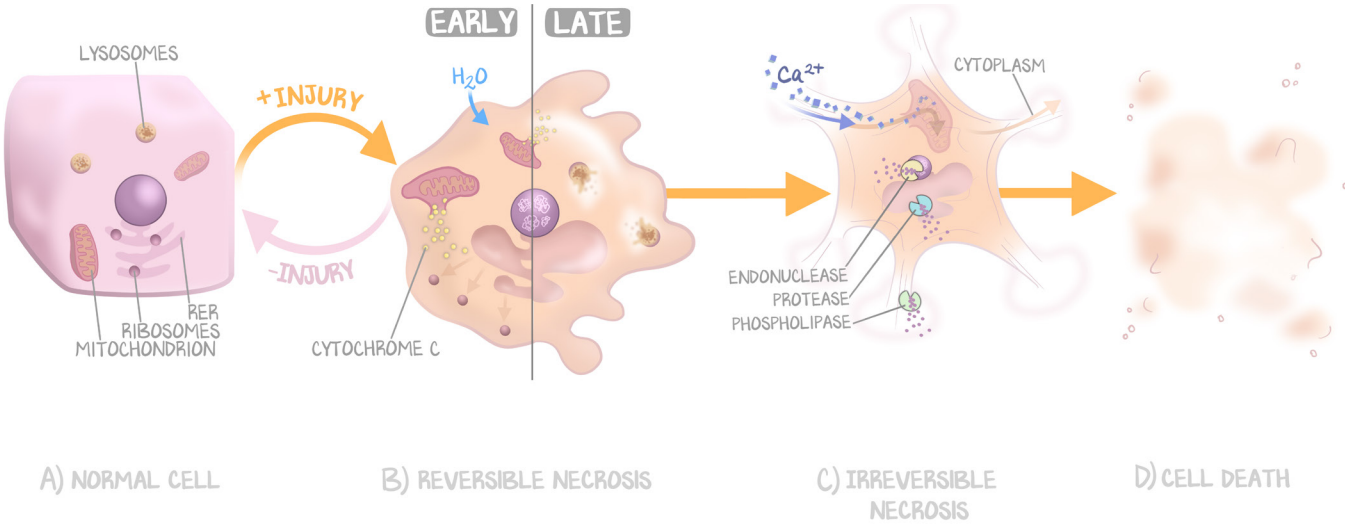


Figure 2.6: Cell Injury and Response to Hypoxemia
(a) A normal cell suffers hypoxemic injury, which begins as reversible. (b) Hypoxemia causes a loss of oxidative phosphorylation and ATP, leading to a loss of Na^+/K^+-ATPase and Ca^{2+} pumps. Fluid enters the cell, resulting in swelling, mitochondrial swelling, and cell-membrane blebbing. The nuclear material clumps. (c) Irreversible cell injury occurs after prolonged hypoxemia, with rupture of the plasma membrane releasing cytoplasm and destroying ionic gradients, the mitochondria rupturing releasing cytochrome c, and the initiation of degradative enzymes that digest proteins and nuclear material. (d) The cell dies.

Citations

Figures 2.2(a), 2.2(b), 2.2(c), 2.3(a), 2.3(b), 2.3(c), 2.4(a), 2.4(b), 2.5(a), 2.5(b), 2.5(c) Originating from the University of Alabama at Birmingham, Department of Pathology PEIR Digital Library at http://peir.net pursuant to a license granted by The UAB Research Foundation.